

Europäisches Patentamt
European Patent Office
Office européen des brevets



(11) **EP 0 666 079 B1**

(12)

EUROPEAN PATENT SPECIFICATION

(45) Date of publication and mention
of the grant of the patent:
07.11.2001 Bulletin 2001/45

(51) Int Cl.7: **A61K 31/53**, A61K 31/505
// C07D487/04

(21) Application number: **94921793.9**

(86) International application number:
PCT/JP94/01196

(22) Date of filing: **20.07.1994**

(87) International publication number:
WO 95/03806 (09.02.1995 Gazette 1995/07)

(54) **REMEDY FOR PARKINSON'S DISEASE**

Arzneimittel gegen Parkinsonsche Krankheit

REMEDE CONTRE LA MALADIE DE PARKINSON

(84) Designated Contracting States:
**AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL
PT SE**

(30) Priority: **27.07.1993 JP 18429593**

(43) Date of publication of application:
09.08.1995 Bulletin 1995/32

(73) Proprietor: **KYOWA HAKKO KOGYO CO., LTD.**
Chiyoda-ku, Tokyo 100 (JP)

(72) Inventors:

- **SUZUKI, Fumio**
Shizuoka 411 (JP)
- **SHIMADA, Junichi**
Shizuoka 411 (JP)
- **KOIKE, Nobuaki**
Shizuoka 411 (JP)
- **ICHIKAWA, Shunji**
Shizuoka 419-01 (JP)
- **NAKAMURA, Joji**
Shizuoka 411 (JP)
- **KANDA, Tomoyuki**
London W13 8DR (GB)
- **KITAMURA, Shigeto**
Tokyo 194 (JP)

(74) Representative: **Harding, Charles Thomas et al**
D. Young & Co.
21 New Fetter Lane
London EC4A 1DA (GB)

(56) References cited:
EP-A- 0 515 107 **JP-A- 5 097 855**
JP-A- 61 165 386 **JP-A- 62 135 475**
JP-T- 1 500 996

- **JIANG ET AL.: "Potentiation of Antiparkinsonin Effects of Dopamine Agonists by Adenosine Antagonists in 6-Hydroxydopamine-Lesioned Rats" NEUROLOGY, vol. 43, no. 4 suppl 2, 1993, page a154 XP002046588**
- **JIANG ET AL.: "Adenosine receptor antagonists potentiate dopamine receptor agonist-induced rotational behavior in 6-hydroxydopamine-lesioned rats." BRAIN RES., vol. 613, no. 2, 1993; pages 347-351, XP002046589**
- **WILLIAMS M.: "Purinergic Drugs: Opportunities in the 1990s" DRUG DEV. RES., vol. 28, no. 3, 1993, pages 438-444, XP002046590**

Note: Within nine months from the publication of the mention of the grant of the European patent, any person may give notice to the European Patent Office of opposition to the European patent granted. Notice of opposition shall be filed in a written reasoned statement. It shall not be deemed to have been filed until the opposition fee has been paid. (Art. 99(1) European Patent Convention).

EP 0 666 079 B1

Best Available Copy

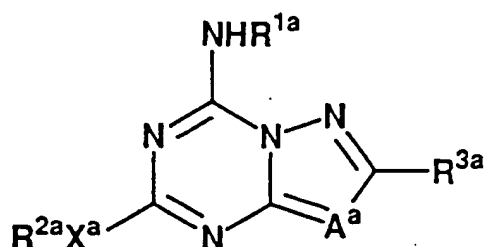
Description

Technical Field

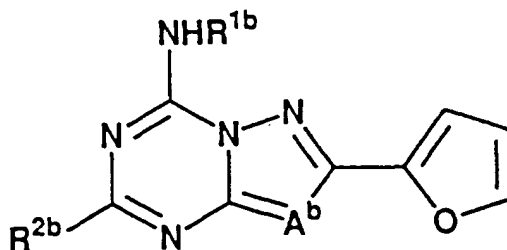
[0001] The present invention relates to a therapeutic agent for Parkinson's disease.

Background Art

[0002] In connection with Compounds (I) (described afterward) in the present invention, it is known that compounds represented by the following formula

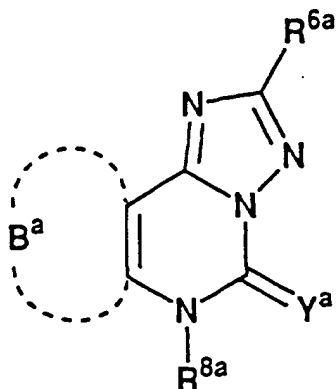


in which R^{1a} represents hydrogen, substituted or unsubstituted lower alkyl, or lower alkanoyl, R^{2a} represents hydrogen, lower alkenyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted phenyl, substituted or unsubstituted aralkyl, or a substituted or unsubstituted heterocyclic group, R^{3a} represents a substituted or unsubstituted 5-membered heterocyclic group, X^a represents O, S, $\text{S}(\text{O})$, $\text{S}(\text{O})_2$, or NR^{4a} (in which R^{4a} represents hydrogen, or substituted or unsubstituted lower alkyl, or R^{2a} and NR^{4a} are combined to form a substituted or unsubstituted 4 to 6-membered saturated heterocyclic group), and A^a represents N or CR^{5a} (in which R^{5a} represents hydrogen, or substituted or unsubstituted lower alkyl), and compounds represented by the following formula



in which R^{1b} represents hydrogen, substituted or unsubstituted lower alkyl, or lower alkanoyl, R^{2b} represents substituted or unsubstituted lower alkyl, lower alkenyl, lower alkynyl, substituted or unsubstituted phenyl, or a substituted or unsubstituted 5- or 6-membered heterocyclic group, and A^b represents N or CR^{5b} (in which R^{5b} represents hydrogen, or substituted or unsubstituted lower alkyl), have a selective adenosine A_2 antagonistic activity (Japanese Published Unexamined Patent Application No. 97855/93 and EP 515107A).

[0003] Further, in connection with Compounds (II) (described afterward), it is known that compounds represented by the following formula



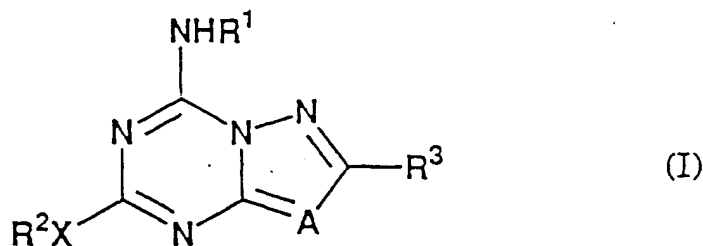
in which R^{6a} represents substituted or unsubstituted phenyl, or a substituted or unsubstituted heterocyclic group, Y^a represents O, S, or NR^{7a} (in which R^{7a} represents hydrogen, substituted or unsubstituted lower alkyl, lower alkenyl, lower alkynyl, substituted or unsubstituted cycloalkyl, or substituted or unsubstituted aryl), R^{8a} represents hydrogen, substituted or unsubstituted lower alkyl, lower alkenyl, substituted or unsubstituted aryl, or substituted or unsubstituted aralkyl, and B^a and the adjacent two carbon atoms are combined to form a substituted or unsubstituted, saturated or unsaturated, monocyclic or bicyclic, carbocyclic or heterocyclic group, have an adenosine A₂ antagonistic activity and exhibits an antispasmodic activity and a bronchodilating activity [Japanese Published Unexamined Patent Application Nos. 165386/86 and 135475/87, J. Med. Chem., 31, 1014 (1988)].

[0004] Research by Jiang et al (Brain Research, 613, 1993, 347-351) has shown that a denosine receptor antagonists potentiate dopamine receptor agonist-induced rotational behaviour in 6-hydroxydopamine-lesioned rats.

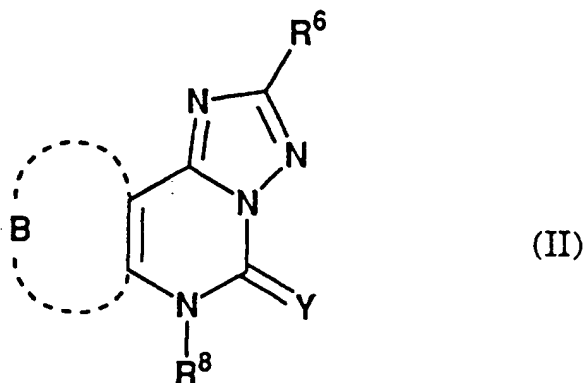
[0005] Furthermore, Williams (Drug Development Research 28: 438-444, 1993) also suggests that A_{2a} receptor ligands because of their unique co-localisation with D₂ receptor containing neurones in the striatopallidial pathway of the basal ganglia may have potential use in the treatment of diseases involving dopaminergic malfunction.

Disclosure of the Invention

[0006] The present invention relates to a therapeutic agent for Parkinson's disease containing as an active ingredient a polycyclic compound, or a pharmaceutically acceptable salt thereof, the compound being represented by the following Formula (I) :



in which, R¹ represents hydrogen, substituted or unsubstituted lower alkyl, or substituted or unsubstituted lower alkanoyl; R² represents hydrogen, substituted or unsubstituted lower alkyl, substituted or unsubstituted lower alkenyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted aralkyl, or a substituted or unsubstituted heterocyclic group; R³ represents a substituted or unsubstituted heterocyclic group; X represents a single bond, O, S, S(O), S(O)₂, or NR⁴ (in which R⁴ represents hydrogen, or substituted or unsubstituted lower alkyl; or R² and NR⁴ are combined to form a substituted or unsubstituted 4 to 6-membered saturated heterocyclic group); and A represents N or CR⁵ (in which R⁵ represents hydrogen, or substituted or unsubstituted lower alkyl), or represented by the following Formula (II):



in which R^6 represents substituted or unsubstituted aryl, or a substituted or unsubstituted heterocyclic group; Y represents O, S, or NR^7 (in which R^7 represents hydrogen, substituted or unsubstituted lower alkyl, substituted or unsubstituted cycloalkyl, or substituted or unsubstituted aryl); R^8 represents hydrogen, substituted or unsubstituted lower alkyl, substituted or unsubstituted lower alkenyl, substituted or unsubstituted lower alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted aralkyl, or a substituted or unsubstituted heterocyclic group; and B and the adjacent two carbon atoms are combined to form a substituted or unsubstituted, partially saturated or unsaturated, monocyclic or bicyclic, carbocyclic or heterocyclic group.

[0007] The compounds represented by Formula (I) and Formula (II) are hereinafter referred to as Compound (I) and Compound (II), respectively, and the same applies to the compounds of other formula numbers.

[0008] In the definitions of the groups in Formula (I) and Formula (II), the lower alkyl means a straight-chain or branched alkyl group having 1 to 6 carbon atoms such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, secbutyl, tert-butyl, pentyl, neopentyl, and hexyl. The lower alkanoyl means a straight-chain or branched alkanoyl group having 1 to 7 carbon atoms such as formyl, acetyl, propionyl, butyryl, isobutyryl, pivaloyl, and hexanoyl. The lower alkenyl means a straight-chain or branched alkenyl group having 2 to 6 carbon atoms such as vinyl, 1-methylvinyl, 1-propenyl, 2-propenyl, 1-butenyl, 2-methyl-1-propenyl, 1,3-butadienyl, 1-pentenyl, 4-pentenyl, 1-hexenyl, 1,4-hexadienyl, and 5-hexenyl. The lower alkynyl means a straight-chain or branched alkynyl group having 2 to 4 carbon atoms such as ethynyl, 1-propynyl, 2-propynyl, 1-butyne, and 2-butyne. The cycloalkyl means a cycloalkyl group having 3 to 8 carbon atoms such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl, a bicycloalkyl group having 7 to 12 carbon atoms such as norbornyl, or a tricycloalkyl group having 7 to 12 carbon atoms. Examples of the aryl are phenyl, naphthyl, indenyl, and anthryl. The aralkyl means an aralkyl group having 7 to 15 carbon atoms such as benzyl, 1-phenylethyl, 2-phenylethyl, 2-phenylpropyl, and diphenylmethyl. Examples of the heterocyclic group are furyl, thienyl, pyrrolyl, pyran, thiopyran, pyridyl, oxazolyl, thiazolyl, imidazolyl, pyrimidyl, triazinyl, indolyl, quinolyl, purinyl, benzoxazolyl, benzothiazolyl, and benzimidazolyl. Examples of the 4 to 6-membered saturated heterocyclic group are azetidino, pyrrolidino, morpholino, and thiomorpholino. Examples of the partially saturated or unsaturated, monocyclic or bicyclic carbocyclic group are cyclopentene, cyclohexene, cycloheptene, and 1,4-dihydronaphthalene. Examples of the partially saturated or unsaturated, monocyclic or bicyclic heterocyclic group are piperidine, tetrahydrobenzo[b]thiophene, isoxazole, oxazole, thiazole, pyrazole, furan, thiophene, pyrrole, pyran, thiopyran, dithine, pyrimidine, imidazole, and benzimidazole.

[0009] The substituted lower alkyl, the substituted lower alkanoyl, the substituted lower alkenyl, the substituted lower alkynyl, the substituted cycloalkyl, the substituted aryl, the substituted aralkyl, the substituted heterocyclic group, the substituted 4 to 6-membered saturated heterocyclic group, and the substituted partially saturated or unsaturated, monocyclic or bicyclic, carbocyclic or heterocyclic group each has 1 to 3 independently-selected substituents. Examples of the substituents are lower alkyl, hydroxy, hydroxy-lower alkyl, halogeno-lower alkyl, lower alkoxy, lower alkoxy-carbonyl, lower alkylthio, lower alkylsulfanyl, lower alkylsulfonyl, aryloxy, aralkyloxy, halogeno-aryloxy, halogeno-aralkyloxy, carboxy, carbamoyl, lower alkanoyl, aroyl, aryl, halogen, nitro, amino, cyano, trifluoromethyl, and substituted or unsubstituted aralkyl. The lower alkyl and the lower alkyl moiety of the hydroxy-lower alkyl, halogeno-lower alkyl, the lower alkoxy, the lower alkoxy-carbonyl, the lower alkylthio, the lower alkylsulfanyl, and the lower alkylsulfonyl have the same meaning as the lower alkyl defined above. The aryl and the aryl moiety of the aryloxy, halogeno-aryloxy, and the aroyl have the same meaning as the aryl defined above. The aralkyl and the aralkyl moiety of the aralkyloxy and halogeno-aralkyloxy have the same meaning as the aralkyl defined above. The lower alkanoyl has the same meaning as the lower alkanoyl defined above. The halogen and the halogen moiety of the halogeno-lower alkyl, the halogenoaryloxy, and the halogeno-aralkyloxy include fluorine, chlorine, bromine, and iodine. Examples of the substituents of the sub-

stituted aralkyl are lower alkyl, hydroxy, and halogen, and the lower alkyl and the halogen have the same meanings as the lower alkyl defined above and the halogen defined above, respectively.

[0010] The above-mentioned pharmaceutically acceptable salts of Compounds (I) and Compounds (II) include pharmaceutically acceptable acid addition salts, metal salts, ammonium salts, organic amine addition salts, and amino acid addition salts.

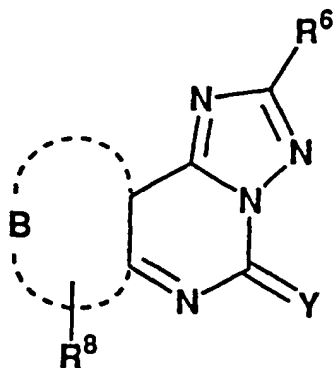
[0011] Examples of the pharmaceutically acceptable acid addition salts of Compounds (I) and Compounds (II) are inorganic acid addition salts such as hydrochloride, sulfate, and phosphate, and organic acid addition salts such as acetate, maleate, fumarate, tartrate, and citrate. Examples of the pharmaceutically acceptable metal salts are alkali metal salts such as sodium salt and potassium salt, alkaline earth metal salts such as magnesium salt and calcium salt, aluminium salt, and zinc salt. Examples of the pharmaceutically acceptable ammonium salts are ammonium salt and tetramethyl ammonium salt. Examples of the pharmaceutically acceptable organic amine addition salts are salts with morpholine and piperidine. Examples of the pharmaceutically acceptable amino acid addition salts are salts with lysine, glycine, and phenylalanine.

[0012] Compounds (I) and Compounds (II) including novel compounds can be produced according to the methods disclosed in the above-described literatures or similar methods thereto. The desired compounds in the processes can be isolated and purified by purification methods conventionally used in organic synthetic chemistry, for example, filtration, extraction, washing, drying, concentration, recrystallization, and various kinds of chromatography.

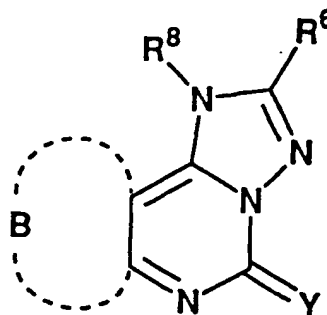
[0013] In the case where a salt of Compound (I) or Compound (II) is desired and it is produced in the form of the desired salt, it can be subjected to purification as such. In the case where Compound (I) or Compound (II) is produced in the free state and its salt is desired, Compound (I) or Compound (II) is dissolved or suspended in a suitable solvent, followed by addition of an acid or a base to form a salt.

[0014] Compounds (I), Compounds (II), and pharmaceutically acceptable salts thereof may be in the form of adducts with water or various solvents, which can also be used as the therapeutic agents of the present invention.

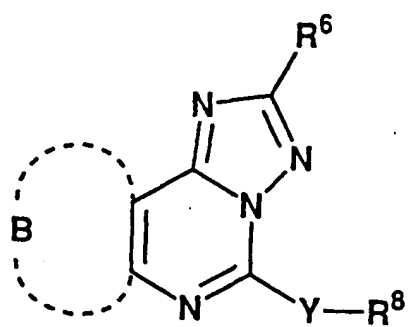
[0015] Some of Compounds (I) and Compounds (II) can exist in the form of optical isomers, and all possible stereoisomers including the above-mentioned ones and mixtures thereof can also be used as the therapeutic agents of the present invention. With regard to Compounds (II), isomers represented by Formula (IIb), Formula (IIc), and Formula (IId) illustrated below can exist, and all these isomers can also be used as the therapeutic agents of the present invention.



(IIb)



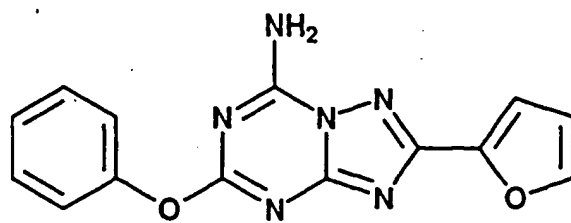
(IIc)



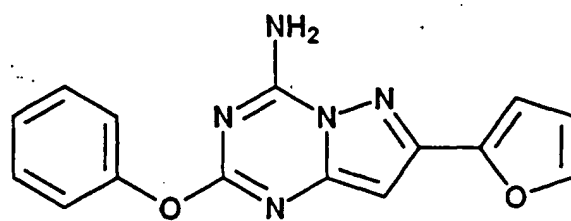
[0016] (In the formulae, R^6 , R^8 , Y, and B have the same meanings as defined above.)

[0017] Examples of Compound (I) and Compound (II) are shown in Table 1.

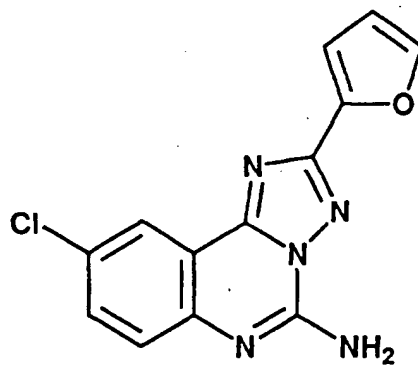
Table 1



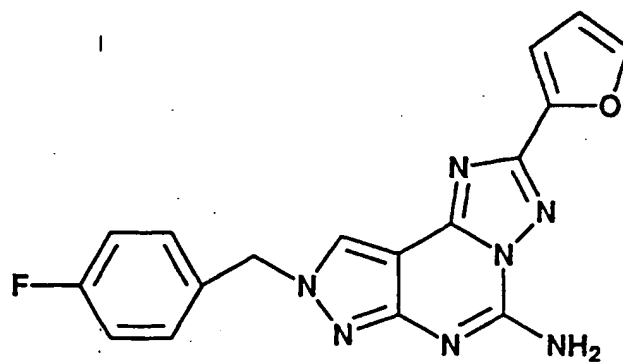
(Compound 1)



(Compound 2)



(Compound 3)



(Compound 4)

Compound 1: 7-Amino-2-(2-furyl)-5-phenoxy[1,2,4]triazolo-[1,5-a]-1,3,5-triazine (compound disclosed in Example 1 of Japanese Published Unexamined Patent Application No. 97855/93)

[0018] Melting Point: 250.7-251.7°C

Elemental Analysis: C ₁₄ H ₁₀ N ₆ O ₂			
Calcd. (%)	C, 57.14;	H, 3.43;	N, 28.56
Found (%)	C, 56.89;	H, 3.36;	N, 28.35

NMR (DMSO-d₆) δ (ppm): 9.00(2H, brs), 7.92(1H, d, J=1.5Hz), 7.49-7.43(2H, m), 7.28-7.23(3H, m), 7.12 (1H, d, J=3.0Hz), 6.70(1H, dd, J=1.5, 3.0Hz)

Compound 2: 7-Amino-2-(2-furyl)-5-phenoxy-pyrazolo[2,3-a]-1,3,5-triazine (compound disclosed in Example 119 of Japanese Published Unexamined Patent Application No. 97855/93)

[0019] Melting Point: 274.1-276.2°C

Elemental Analysis: C ₁₅ H ₁₁ N ₅ O ₂ ·1/4H ₂ O			
Calcd. (%)	C, 60.50;	H, 3.89;	N, 23.52
Found (%)	C, 60.69;	H, 3.54;	N, 23.61

IR (KBr) ν_{max} (cm⁻¹): 1664, 1603, 1552 NMR (DMSO-d₆) δ (ppm): 8.82(1H, brs), 8.46(1H, brs), 7.84(1H, d, J=1.0Hz), 7.47-7.41(2H, m), 7.28-7.21 (3H, m), 7.00(1H, d, J=3.0Hz), 6.66(1H, dd, J=1.0, 3.0Hz), 6.43(1H, s)

Compound 3: 5-Amino-9-chloro-2-(2-furyl)-1,2,4-triazolo-[1,5-c]quinazoline (compound disclosed in Example 33 of Japanese Published Unexamined Patent Application No. 165386/86)

[0020] Melting Point : 257-259°C

Elemental Analysis: C ₁₃ H ₈ ClN ₅ O·0.4(CH ₃) ₂ NCHO			
Calcd. (%)	C, 54.16;	H, 3.46;	N, 24.02
Found (%)	C, 53.90;	H, 3.31;	N, 24.09

IR (KBr) ν_{max} (cm⁻¹): 1682, 1614, 1589, 1555, 1528, 1480

NMR (DMSO-d₆) δ (ppm): 8.17(1H, d, J=2.5Hz), 8.02(2H, brs), 7.99-7.98(1H, m), 7.71(1H, dd, J=2.5, 8.7Hz), 7.57(1H, d, J=8.7Hz), 7.28(1H, d, J=3.5Hz), 6.76(1H, dd, J=2.5, 3.5Hz)

¹³C NMR (DMSO-d₆) δ (ppm): 155.6, 150.8, 145.2, 144.9, 143.7, 132.2, 126.9, 126.8, 122.1, 114.1, 112.3, 112.1

Compound 4: 5-Amino-8-(4-fluorobenzyl)-2-(2-furyl)pyrazolo-[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine [compound 18f disclosed in Eur. J. Med. Chem., 28, 569 (1993)]

[0021]

Melting Point: 276.1-277.8°C

FAB-MS(M/Z) : 350(M⁺+H)

IR (KBr) ν_{max} (cm⁻¹): 1689, 1680, 1621, 1528, 1515, 1225

NMR (DMSO-d₆) δ (ppm): 8.75(1H, s), 7.94(1H, d, J=0.7Hz), 7.64(2H, s), 7.43-7.38(2H, m), 7.23-7.16 (3H, m), 6.74-6.73(1H, m), 5.49(2H, s)

[0022] The pharmacological activities of Compound (I) and Compound (II) are shown below by experimental examples.

Experimental Example 1

Effect on Locomotor Activity in Parkinson's Disease Model in Mice

[0023] 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) causes symptoms of Parkinson's disease in humans

[Science, 219, 979 (1983)]. It is reported that an experimental Parkinson's disease model was obtained by administering MPTP to mice [Science, 224, 1451 (1984)]. If a compound is effective on the experimental Parkinson's disease model in mouse, the compound can be expected to have a therapeutic effect on Parkinson's disease.

[0024] The experiment was performed by using several groups of 7-weeks-old male C57BL/6 mice (weighing 20 to 24 g, Japan SLC), each group consisting of 8 mice. MPTP (RBI Co., Ltd.) dissolved in a physiological saline solution (Otsuka Pharmaceutical Co., Ltd.) was intraperitoneally administered to each mouse once a day for five consecutive days at a dose of 30 mg/kg. Test compounds were suspended in injectable distilled water (Otsuka Pharmaceutical Co., Ltd.) containing Tween 80 [polyoxyethylene (20) sorbitan monooleate]. L-DOPA (Kyowa Hakko Kogyo Co., Ltd.) was suspended in 0.3% CMC (sodium carboxymethylcellulose). Thirty minutes after the final MPTP administration, the test compound suspensions and the control suspension [injectable distilled water (Otsuka Pharmaceutical Co., Ltd.) containing Tween 80] containing no test compound were orally administered to separate groups of the mice (0.1 ml per 10 g of body weight). The amount of active movements of each mouse was measured by using Automex-II (Columbus Instruments International Corp.) for the period of 30 minutes starting 30 minutes after the administration of the test compound. The effect of the compounds was evaluated by comparing the average counts of the active movements of the test compound-administered groups with those of the control groups. Statistical comparison of the values was carried out by Williams-Wilcoxon test.

[0025] The results are shown in Table 2.

Table 2

Group	Administration	Dose of Test Compound (mg/kg)	Amount of Active Movements (average count \pm S.E.M)
Normal Control	MPTP (-)		
	Test Compound (-)	-	1984 \pm 122.3
MPTP	MPTP (+)		
	Test Compound (-)	-	41 \pm 14.3 ##
Compound 1	MPTP (+)		
	Compound 1 (+)	10	785 \pm 87.3 **
Normal Control	MPTP (-)		
	Test Compound (-)	-	1875 \pm 77.7
MPTP	MPTP (+)		
	Test Compound (-)	-	207 \pm 85.5 ##
L-DOPA	MPTP (+)		
	L-DOPA (+)	300	561 \pm 271.01 ¹⁾

##: p<0.01 (comparison with normal control group)

**: p<0.01 (comparison with MPTP-treated group)

1): no significant difference as compared with MPTP-treated group)

Experimental Example 2 Effect on Haloperidol-Induced Catalepsy

[0026] The experiment was performed by using several groups of 5-weeks-old male ddY mice (weighing 22 to 24 g, Japan SLC), each group consisting of 5 mice. Haloperidol (Janssen Pharmaceutica) suspended in 0.3% CMC was intraperitoneally administered to each mouse at a dose of 1.0 mg/kg. Test compounds were suspended in 0.3% CMC or in injectable distilled water (Otsuka Pharmaceutical Co., Ltd.) containing Tween 80. L-DOPA (Kyowa Hakko Kogyo Co., Ltd.) and benserazide hydrochloride (Kyowa Hakko Kogyo Co., Ltd.) were suspended in 0.3% CMC. One hour after the haloperidol administration, the test compound suspensions and the control suspension [injectable distilled water (Otsuka Pharmaceutical Co., Ltd.) containing Tween 80] containing no test compound were orally administered to separate groups of the mice (0.1 ml per 10 g of body weight). One hour after the administration of the test compound, the forelimbs of each mouse and subsequently the hindlimbs of the same mouse were placed on a 4.5 cm-high, 1.0 cm-wide bar and catalepsy was estimated. All of the test compounds were orally administered at a dose of 10 mg/kg, and L-DOPA (100 mg/kg) and benserazide (25 mg/kg) were intraperitoneally administered together as a control experiment. The catalepsy score and the standard of judgment are shown below.

score	duration of the cataleptic posture	
0	forelimbs	less than 5 seconds
	hindlimbs	less than 5 seconds
1	forelimbs	from 5 (inclusive) to 10 (exclusive) seconds
	hindlimbs	less than 5 seconds
2	forelimbs	10 seconds or more
	hindlimbs	less than 5 seconds
3	forelimbs	from 5 (inclusive) to 10 (exclusive) seconds
	hindlimbs	from 5 (inclusive) to 10 (exclusive) seconds;
4	or forelimbs	less than 5 seconds
	hindlimbs	5 seconds or more
5	forelimbs	10 seconds or more
	hindlimbs	from 5 (inclusive) to 10 (exclusive) seconds;
6	or forelimbs	from 5 (inclusive) to 10 (exclusive) seconds
	hindlimbs	10 seconds or more
7	forelimbs	10 seconds or more
	hindlimbs	10 seconds or more

[0027] The effect of the compounds was evaluated by the total of the catalepsy scores of five mice in each group (25 points at the full). The groups wherein the total score was not more than 20 points were estimated to be effective. The number of the animals showing remission against catalepsy is the number of the mice for which the catalepsy score was not more than 4 points. The remission rate shows the rate of decrease in total score based on that of the control group.

[0028] The ED₅₀ (50% effective dose) values were determined using ten mice at each dose. A test compound was judged to be effective at the dose where the catalepsy score was 3 or less than 3. The ED₅₀ values were calculated by Probit analysis.

[0029] The results are shown in Table 3.

Table 3

Compound No.	Total Score	Number of the Animals Showing Remission	Remission Rate (%)	ED ₅₀ (mg/kg)
0.3% Tween 80 (Control)	25	0	0	
L-DOPA + benserazide	18	4	28	107.5
1	5	5	80	1.3
2	17	4	32	
3	13	4	48	
4	12	3	52	

Experimental Example 3 Augmentation of the Contralateral Rotation in Rats with a 6-Hydroxydopamine-Induced Unilateral Lesion of the Nigrostriatal Dopamine Pathway

[0030] When a unilateral lesion of the nigrostriatal pathway is induced by 6-hydroxydopamine in rodents, the sensitivity of dopamine receptors in the denervated striatum is enhanced. Administration of a dopamine agonist to the rodents in such a condition induces a rotational behavior to the side contralateral to the lesioned side [Acta Physiol. Scand., 367, 69 (1971)]. This model has been used for a long time as a model for the study of Parkinson's disease and in the screening of drugs for this disease [Neurol. Neurobiol.; 33, 1 (1987)].

[0031] Male Sprague-Dawley rats (weighing 200 to 240 g, Japan SLC) were pretreated with desipramine hydrochloride (25 mg/kg, i.p., Sigma Co.) 30 minutes before surgery to protect noradrenergic neurons. Then, the animals were anesthetized with sodium pentobarbital (30 mg/kg, i.p., Dainippon Pharm. Co., Ltd.) and the nigrostriatal pathway was

lesioned by injection of 6-hydroxydopamine hydrobromide (8 µg, Sigma Co.) into the left medial forebrain bundle. 6-Hydroxydopamine hydrobromide was dissolved in physiological saline containing 0.05% L-ascorbic acid (Wako Pure Chem. Industries, Ltd.) to make 2 µl of solution and injected over 3 minutes.

[0032] More than 10 days after surgery, each rat was placed in a plastic bowl (30 cm in diameter). Apomorphine (0.1 mg/kg, Sandoz, AG) was injected subcutaneously and the rats which showed a rotational behavior to the side contralateral to the lesioned side at a frequency of more than 600 counts/60 minutes after apomorphine administration were used for screening. The number of rotations was counted with an automated rotometer, in which each 180° turn was counted as a rotation.

[0033] Test compounds were suspended in 0.3% sodium carboxymethylcellulose and administered orally at a dose of 10 mg/kg 30 minutes before the injection of apomorphine (0.1 mg/kg, s.c.). The counts of rotations were summed up every 5 minutes for 150 minutes after apomorphine administration. The total rotation counts induced by apomorphine (0.1 mg/kg, s.c.) with and without a test compound were statistically compared, using the same animals. Rats were allowed to rest more than 5 days between each experiment. Statistical comparison of the values was carried out by Sign-Wilcoxon test.

[0034] The results are shown in Table 4.

Table 4

Compd. No.	total rotation counts (average count ± S.E.M.)	
	apomorphine	test compound + apomorphine
1	706 ± 59	1011 ± 139*

*: p<0.05

Experimental Example 4 Acute Toxicity Test

[0035] Test compounds were orally administered to groups of dd-strain male mice weighing 20 ± 1 g, each group consisting of three mice. Seven days after the administration, minimum lethal dose (MLD) of each compound was determined by observing the mortality.

[0036] The MLD values of Compound 1 and Compound 2 are greater than 300 mg/kg, indicating that the toxicity of the compounds is weak. Therefore, these compounds can be safely used in a wide range of doses.

[0037] Compound (I), Compound (II), and pharmaceutically acceptable salts thereof exhibit antiparkinsonism activity, and are useful as a therapeutic agent for Parkinson's disease.

[0038] Compound (I), Compound (II), and pharmaceutically acceptable salts thereof can be administered as they are, or in the form of various pharmaceutical compositions. The pharmaceutical compositions in accordance with the present invention can be prepared by uniformly mixing an effective amount of Compound (I), Compound (II), or a pharmaceutically acceptable salt thereof, as an active ingredient, with a pharmaceutically acceptable carrier. It is desired that such pharmaceutical compositions are prepared in a unit dose form suitable for oral administration or administration through injection.

[0039] For preparing a pharmaceutical composition for oral administration, any useful pharmaceutically acceptable carrier can be used. For example, liquid preparations for oral administration such as suspension and syrup can be prepared using water, sugars such as sucrose, sorbitol, and fructose, glycols such as polyethylene glycol and propylene glycol, oils such as sesame oil, olive oil, and soybean oil, preservatives such as p-hydroxybenzoates, flavors such as strawberry flavor and peppermint, and the like. Powders, pills, capsules, and tablets can be prepared using excipients such as lactose, glucose, sucrose, and mannitol, disintegrating agents such as starch and sodium alginate, lubricants such as magnesium stearate and talc, binders such as polyvinyl alcohol, hydroxypropyl cellulose, and gelatin, surfactants such as fatty acid esters, plasticizers such as glycerin, and the like. Tablets and capsules are the most useful oral unit dose forms because of the readiness of administration. For preparing tablets and capsules, solid pharmaceutical carriers are used.

[0040] Injectable preparations can be prepared using a carrier such as distilled water, a salt solution, a glucose solution, or a mixture of a salt solution and a glucose solution. The preparations can be prepared in the form of solution, suspension or dispersion according to a conventional method by using a suitable auxiliary.

[0041] Compound (I), Compound (II), and pharmaceutically acceptable salts thereof can be administered orally or parenterally as injections in the said dosage forms. The effective dose and the administration schedule vary depending upon the mode of administration, the age, body weight, and conditions of a patient, etc. However, generally, Compound (I), Compound (II), or a pharmaceutically acceptable salt thereof is administered in a daily dose of 1 to 50 mg/kg in 3 to 4 parts.

[0042] Certain embodiments of the invention are illustrated in the following examples.

Best Mode For Carrying Out The InventionExample 1 Tablets

[0043] Tablets having the following composition were prepared in a conventional manner.

[0044] Compound 1 (40 g) was mixed with 286.8 g of lactose and 60 g of potato starch, followed by addition of 120 g of a 10% aqueous solution of hydroxypropylcellulose. The resultant mixture was kneaded, granulated, and then dried by a conventional method. The granules were refined to give granules used to make tablets. After mixing the granules with 1.2 g of magnesium stearate, the mixture was formed into tablets each containing 20 mg of the active ingredient by using a tablet maker (Model RT-15, Kikusui) having pestles of 8 mm diameter.

Composition of One Tablet	
Compound 1	20 mg
Lactose	143.4mg
Potato Starch	30 mg
Hydroxypropylcellulose	6 mg
Magnesium Stearate	0.6mg
	200 mg

Example 2 Fine Granules

[0045] Fine granules having the following composition were prepared in a conventional manner.

[0046] Compound 2 (20 g) was mixed with 655 g of lactose and 285 g of corn starch, followed by addition of 400 g of a 10% aqueous solution of hydroxypropylcellulose. The resultant mixture was kneaded, granulated, and then dried by a conventional method to give fine granules containing 20 g of the active ingredient in 1,000 g.

Composition of One Pack of Fine Granules	
Compound 2	20 mg
Lactose	655 mg
Corn Starch	285 mg
Hydroxypropylcellulose	40 mg
	1,000 mg

Example 3 Capsules

[0047] Capsules having the following composition were prepared in a conventional manner.

[0048] Compound 3 (200 g) was mixed with 995 g of Avicel and 5 g of magnesium stearate. The mixture was put in hard capsules No. 4 each having a capacity of 120 mg by using a capsule filler (Model LZ-64, Zanashi) to give capsules each containing 20 mg of the active ingredient.

Composition of One Capsule	
Compound 3	20 mg
Avicel	99.5mg
Magnesium Stearate	0.5mg
	120 mg

Example 4 Injections

[0049] Injections having the following composition were prepared in a conventional manner.

[0050] Compound 4 (1 g) was dissolved in 100 g of purified soybean oil, followed by addition of 12 g of purified egg yolk lecithin and 25 g of glycerine for injection. The resultant mixture was made up to 1,000 ml with distilled water for injection, thoroughly mixed, and emulsified by a conventional method. The resultant dispersion was subjected to aseptic filtration by using 0.2 µm disposable membrane filters, and then aseptically put into glass vials in 2 ml portions to give

injections containing 2 mg of the active ingredient per vial.

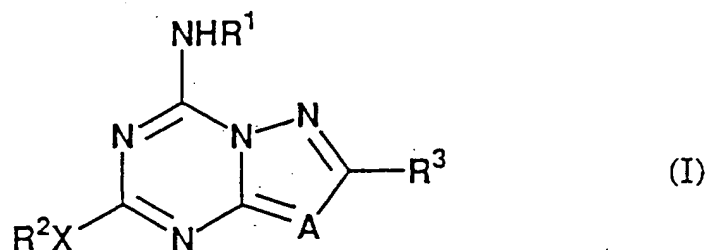
Composition of One Injection Vial	
Compound 4	2 mg
Purified Soybean Oil	200 mg
Purified Egg Yolk Lecithin	24 mg
Glycerine for Injection	50 mg
Distilled Water for Injection	1.72 ml
	2.00 ml

Industrial Applicability

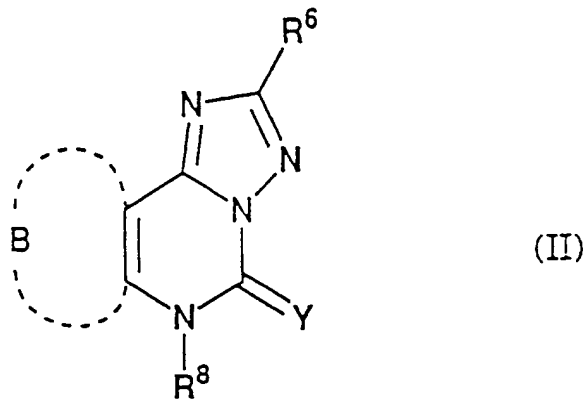
[0051] According to the present invention, there can be provided an excellent therapeutic agent for Parkinson's disease.

Claims

1. The use of a polycyclic compound or a pharmaceutically acceptable salt thereof for the preparation of a pharmaceutical composition for treating Parkinson's disease, either wherein the compound is represented by the following Formula (I):



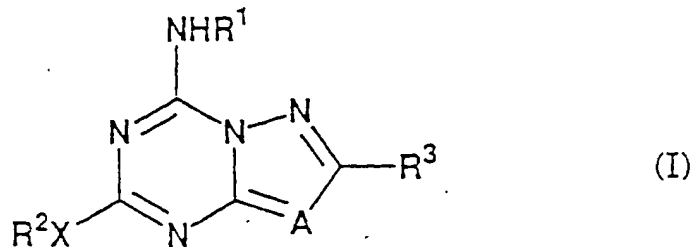
in which, R¹ represents hydrogen, substituted or unsubstituted lower alkyl, or substituted or unsubstituted lower alkanoyl; R² represents hydrogen, substituted or unsubstituted lower alkyl, substituted or unsubstituted lower alkenyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted aralkyl, or a substituted or unsubstituted heterocyclic group; R³ represents a substituted or unsubstituted heterocyclic group; X represents a single bond, O, S, S(O), S(O)₂, or NR⁴ (in which R⁴ represents hydrogen, or substituted or unsubstituted lower alkyl; or R² and NR⁴ are combined to form a substituted or unsubstituted 4 to 6-membered saturated heterocyclic group); and A represents N or CR⁵ (in which R⁵ represents hydrogen, or substituted or unsubstituted lower alkyl), or wherein the compound is represented by the following Formula (II):



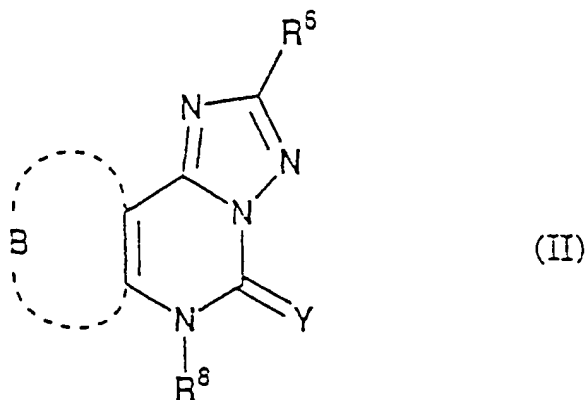
in which R^6 represents substituted or unsubstituted aryl, or a substituted or unsubstituted heterocyclic group; Y represents O, S, or NR^7 (in which R^7 represents hydrogen, substituted or unsubstituted lower alkyl, substituted or unsubstituted cycloalkyl, or substituted or unsubstituted aryl); R^8 represents hydrogen, substituted or unsubstituted lower alkyl, substituted or unsubstituted lower alkenyl, substituted or unsubstituted lower alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted aralkyl, or a substituted or unsubstituted heterocyclic group; and B and the adjacent two carbon atoms are combined to form a substituted or unsubstituted, partially saturated or unsaturated, monocyclic or bicyclic, carbocyclic or heterocyclic group.

Patentansprüche

1. Verwendung einer polycyclischen Verbindung oder eines pharmazeutisch verträglichen Salzes davon zur Herstellung eines Arzneimittels zur Behandlung der Parkinsonschen Krankheit, wobei die Verbindung entweder durch die folgende Formel (I) wiedergegeben wird



in welcher R^1 für ein Wasserstoffatom, einen substituierten oder unsubstituierten Niederalkyl-, oder substituierten oder unsubstituierten Niederalkanoylrest steht; R^2 ein Wasserstoffatom, einen substituierten oder unsubstituierten Niederalkyl-, substituierten oder unsubstituierten Niederalkenyl-, substituierten oder unsubstituierten Cycloalkyl-, substituierten oder unsubstituierten Aryl-, substituierten oder unsubstituierten Aralkyl-, oder einen substituierten oder unsubstituierten heterocyclischen Rest bedeutet; R^3 für einen substituierten oder unsubstituierten heterocyclischen Rest steht; X eine Einfachbindung, O, S, S(O), S(O)₂ oder NR^4 bedeutet (wobei R^4 ein Wasserstoffatom oder einen substituierten oder unsubstituierten Niederalkylrest bedeutet; oder R^2 und NR^4 unter Bildung eines substituierten oder unsubstituierten 4- bis 6-gliedrigen gesättigten heterocyclischen Rests verbunden sind); und A N oder CR^5 darstellt (wobei R^5 ein Wasserstoffatom oder einen substituierten oder unsubstituierten Niederalkylrest bedeutet), oder wobei die Verbindung durch die folgende Formel (II) wiedergegeben wird

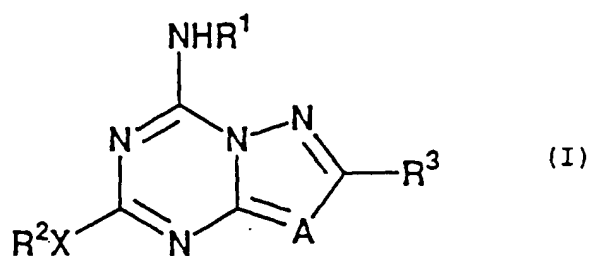


20 in welcher R^6 einen substituierten oder unsubstituierten Aryl-, oder einen substituierten oder unsubstituierten heterocyclischen Rest bedeutet; Y O, S oder NR^7 darstellt (wobei R^7 für ein Wasserstoffatom, einen substituierten oder unsubstituierten Niederalkyl-, substituierten oder unsubstituierten Cycloalkyl-, oder substituierten oder unsubstituierten Arylrest steht); R^8 ein Wasserstoffatom, einen substituierten oder unsubstituierten Niederalkyl-, substituierten oder unsubstituierten Niederalkenyl-, substituierten oder unsubstituierten Niederalkinyl-, substituierten oder unsubstituierten Cycloalkyl-, substituierten oder unsubstituierten Aryl-, substituierten oder unsubstituierten Aralkyl-, oder einen substituierten oder unsubstituierten heterocyclischen Rest bedeutet; und B und die benachbarten beiden Kohlenstoffatome unter Bildung eines substituierten oder unsubstituierten, teilweise gesättigten oder ungesättigten, monocyclischen oder bicyclischen, carbocyclischen oder heterocyclischen Rests verbunden sind.

30 Revendications

1. Utilisation d'un composé polycyclique, ou d'un sel admissible en pharmacie d'un tel composé, pour la préparation d'une composition pharmaceutique destinée au traitement de la maladie de Parkinson, ledit composé étant représenté

35 - soit par la formule suivante (I) :



50 dans laquelle

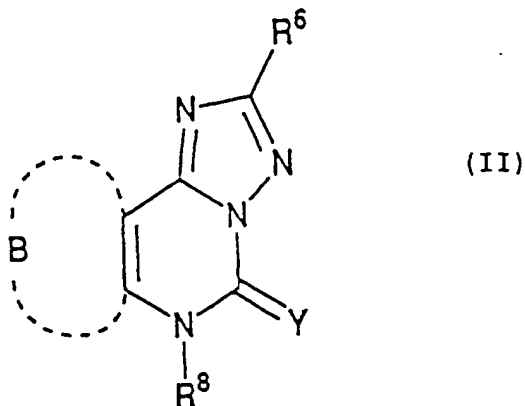
R^1 représente un atome d'hydrogène, un groupe alkyle inférieur portant ou non des substituants ou un groupe alcanoyle inférieur portant ou non des substituants ;

R^2 représente un atome d'hydrogène, un groupe alkyle inférieur portant ou non des substituants, un groupe alcényle inférieur portant ou non des substituants, un groupe cycloalkyle portant ou non des substituants, un groupe aryle portant ou non des substituants, un groupe aralkyle portant ou non des substituants ou un groupe hétérocyclique portant ou non des substituants ;

R^3 représente un groupe hétérocyclique portant ou non des substituants ;

X représente une liaison simple, -O-, -S-, -S(O)-, -S(O)₂-, ou -NR⁴- où R⁴ représente un atome d'hydrogène ou un groupe alkyle inférieur portant ou non des substituants, ou est combiné avec R² pour former un groupe hétérocyclique saturé comportant de 4 à 6 chaînons, portant ou non des substituants ;
et A représente N ou CR⁵ où R⁵ représente un atome d'hydrogène ou un groupe alkyle inférieur portant ou non des substituants ;

- soit par la formule suivante (II)



dans laquelle

R⁶ représente un groupe aryle portant ou non des substituants ou un groupe hétérocyclique portant ou non des substituants ;

Y représente -O-, -S- ou -NR⁷- où R⁷ représente un atome d'hydrogène, un groupe alkyle inférieur portant ou non des substituants, un groupe cycloalkyle portant ou non des substituants, ou un groupe aryle portant ou non des substituants ;

R⁸ représente un atome d'hydrogène, un groupe alkyle inférieur portant ou non des substituants, un groupe alcényle inférieur portant ou non des substituants, un groupe alcynyle inférieur portant ou non des substituants, un groupe cycloalkyle portant ou non des substituants, un groupe aryle portant ou non des substituants, un groupe aralkyle portant ou non des substituants ou un groupe hétérocyclique portant ou non des substituants ;

et B constitue, conjointement avec les deux atomes de carbone adjacents, un groupe carbocyclique ou hétérocyclique, monocyclique ou bicyclique, partiellement saturé ou insaturé, portant ou non des substituants.

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ **BLACK BORDERS**
- ☐ **IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**
- ☐ **FADED TEXT OR DRAWING**
- ☐ **BLURRED OR ILLEGIBLE TEXT OR DRAWING**
- ☐ **SKEWED/SLANTED IMAGES**
- ☐ **COLOR OR BLACK AND WHITE PHOTOGRAPHS**
- ☐ **GRAY SCALE DOCUMENTS**
- ☐ **LINES OR MARKS ON ORIGINAL DOCUMENT**
- ☐ **REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY**
- ☐ **OTHER:** _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.